Non-Oral Etiologies of Oral Malodor and Altered Chemosensation

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A NUMBER OF NON-ORAL CAUSES for oral malodor have been discussed. Several well documented etiologies for non-oral malodor include renal failure, cirrhosis of the liver, and diabetes mellitus. Each of these conditions has been examined using analytical instrumentation. In addition there appear to be several other metabolic conditions involving enzymatic and transport anomalies (such as trimethylaminuria) which lead to the systemic production of volatile malodors that manifest themselves as halitosis and/or altered chemoreception. Our studies include patients who have been referred to us after being examined by numerous clinical specialists with no identification or relief from their problem. This is due in part to the intermittent nature of many of these problems as well as an apparent lack of knowledge concerning many of these metabolic problems and their relation to oral symptoms. *J Periodontol 1992; 63:790–796.*

Key Words: Halitosis/etiology; chemoreceptors, altered; diabetes mellitus; liver cirrhosis; renal failure.

Oral malodor has been the subject of scientific reviews[1-4] and discussion in the popular press. Tonzetich is generally regarded as having defined the nature, abundance, and origin of the volatile sulfur compounds (VSC) that are responsible for endogenous oral malodor.[1,2,5-8] In addition to linking the VSC to endogenous halitosis, the oral health implications of the VSC generated by oral mechanisms have also been explored.[9-11]

Non-oral causes of oral malodor have received attention in the dental literature[2,4,12] particularly because of the clinical importance of early diagnosis. The potential severity of the pathologies which give rise to such odors makes it imperative for the dentist to be informed and aware of the need for patient referral for additional medical examination.

Attia and Marshall[4] have discussed a variety of non-oral conditions which may give rise to "bad breath." Among the host of disorders they list in this review, only a handful have been investigated using analytical techniques to identify the volatile organic compounds associated with the odor. These include such systemic diseases as diabetes mellitus,[13] chronic renal failure,[14] and cirrhosis of the liver,[15-17] which are often cited as examples of how emanations from the oral cavity may serve as non-invasive indicators of systemic metabolism. The compounds identified as characteristic of these disease states are listed in Table 1.

Table 1. Oral Volatiles Identified in Patients with Systemic Pathologies

Pathology	Reference
Diabetes mellitus: (ketonic breath) acetone and other ketones	13
Uremia/kidney failure: (fishy odor) dimethylamine [$(CH_3)_2NH$; trimethylamine $(CH_3)_3N$]	14
Cirrhosis of the liver: (*Fetor Hepaticus*) C_2-C_5 aliphatic acids, methylmercaptan (CH_3SH), ethanethiol (CH_3CH_2SH), and dimethylsulfide ($CH_3S\ CH_3$)	15,16

Missing from Table 1 are a series of inborn errors of metabolism that are associated with an enzyme deficiency or transport problem.[18,19] Many of these disorders present with definitive odors from all body effluvia, including breath. Homozygotics for these disorders are usually diagnosed within the first few days of life, since the metabolic defect may cause permanent brain damage or death. Although the initial diagnosis may be made by olfaction, subsequent confirmation of the odor caused by the disorder is made by gas chromatography (GC) or gas chromatography/mass spectrometry (GC/MS).[19] As will be discussed below, there is a possibility that adults who are heterozygotic for sulfur-containing amino acidurias may present with persistent oral malodor.

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Diseases within the lungs or upper respiratory tract, such as anaerobic infections and/or cancer, are reported to produce malodor that emanates from the oral cavity.[4,20-22] Such clinical reports have largely been anecdotal and/or case reports based upon organoleptic evaluations unaccompanied by identification of the odorants. Nonetheless, numerous volatile components can be isolated and identified in the expired breath of normal individuals.[22-24] These volatiles in expired breath are a mixture of organic compounds originating in both the mouth and the lung.[23,24] Volatiles from the lung are a potentially important source of information for both systemic and lung physiology because they may be derived from endogenous or absorbed volatile substances in blood. In addition, certain substances in lung air are likely to be in equilibrium with alveolar fluids, cells within the lung (including tumor cells), and cells which are attached to the bronchial epithelium, such as alveolar macrophages.

Systematic studies of expired breath have been performed on normal populations[23,24] as well as those suffering from bronchogenic carcinoma. These studies did not report an oral malodor to be correlated with the disease state nor were particularly malodorous compounds found to be indicative of the disease state. However, GC/MS analysis of collected expired air (20 L) of lung cancer patients and controls showed that a group of selected volatiles could distinguish patients from controls.[23] The volatiles that allegedly allowed this discrimination were acetone, methylethylketone, and n-propanol. Preti et al.[24] examined 10 patients with newly diagnosed bronchogenic carcinoma and compared them to both age-matched and youthful control populations. Significantly greater concentrations of o-toluidine were found in the expired lung air of patients with lung cancer than either control group. Aniline was present in half the patient population but not at all in age-matched controls. Overall, however, profiles of constituents from both control groups and patients were remarkably similar, with the significant differences found primarily in the minor components of the mixture.

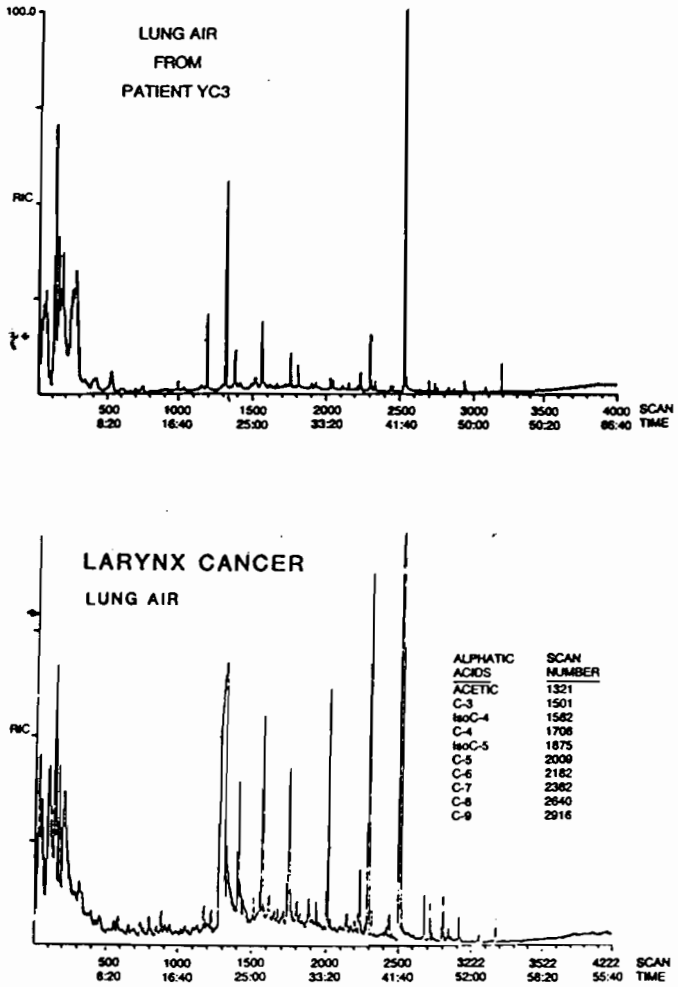

Figure 1. The reconstructed ion chromatograms from the lung air volatiles of a normal patient and one suffering from larynx cancer generated by the data system of the Finnegan/MAT 4510 gas chromatograph/mass spectrometer. Note the similarity in the 2 chromatograms with most large components being similar in each sample. The acids present in the patient with carcinoma elute at the scan numbers indicated in the figure: acetic (1321); propanoic (1501); isobutyric (1582); butyric (1708); isovaleric (1875); valeric (2009); hexanoic (2182); heptanoic (2382); octanoic (2640); and nonanoic (2916).

More germane to the production of malodor may be carcinoma of the upper respiratory tract/oropharyngeal region. McGregor and colleagues[21] likened the oropharynx to the vaginal barrel in the richness of its anaerobic flora and the potential for colonization of squamous cell carcinoma and/or surgical wounds by these organisms. The latter condition was reported by Dankert et al.,[25] who found C_2-C_6 aliphatic acids to be associated with vaginal tumors and wounds colonized by anaerobes. McGregor et al.[21] reported a similar foul odor from oropharyngeal tumors and employed a metronidazole type drug, as did Dankert et al.,[25] to eliminate the foul odor suggesting that a similar group of compounds were present in these tumors.

As noted above, our laboratory has reported on the analysis of expired air from patients suffering from lung carcinoma. Several patients with head and neck carcinoma were also examined. Figure 1 shows the reconstructed ion chromatogram generated from the expired lung air of a normal patient and one suffering from larynx cancer. The latter patient showed a series of C_2-C_9 aliphatic acids, which may explain, in part, the odor physicians have anecdotally reported on the breath of these patients.

In addition to cancer patients, our laboratory has several years experience in analysis of lung and body fluids from patients presenting with persistent, idiopathic malodor production. We use the term idiopathic malodor production since each of the patients we have seen has been evaluated by two or more medical and/or dental specialists with no clinical cause for the odor production having been identified. Although the majority of these patients report that the odor originates in the oral/nasal regions, we have also examined malodor originating in the axillae and genital region.

Examination of these patients is due, in part, to the creation of Chemosensory Clinical Research Centers (CCRC)

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by the National Institutes of Health. Currently, five of these centers are in operation with the express purpose of increasing understanding of the nature and etiologies of smell and taste dysfunctions. The CCRC, established by the Monell Chemical Senses Center in collaboration with Thomas Jefferson Medical College, is the only center to accept referrals of patients with odor production problems, due to our unique analytical capabilities and experience in the analysis of oral volatiles in normal[19,26,27] and pathological states.[12,19,28,29]

Our expertise in body fluid analysis is made available to CCRC patients via our Analytical Core Facility, where we investigate the possible contribution of chemistry to complaints of dysgeusia and/or dysosmia as well as chronic, idiopathic malodor production. Patients are seen by referral from either their dentist or physician; however, these patients have typically been examined by several clinical specialists in an effort to determine the etiology of their complaints.

METHODS AND MATERIALS

Sample Collection and Analysis

Each patient or control seen by the Analytical Core is required to present in a fasted condition wearing no fragrances or cosmetics. Patients referred for chronic malodor production are organoleptically evaluated prior to instrumental analysis to obtain a subjective odor rating by 3 judges (G.P., I-M. Y., and E.W.). Prior to sampling they must equilibrate their mouth air by breathing through their noses for 2 minutes. Collections of mouth air from chronic malodor patients are directly analyzed by aspiration into a gas chromatograph equipped with a flame photometric detector (GC/FPD) via a Teflon tube as discussed by Tonzetich et al.[1,2]

Patients presenting to our facility with complaints of dysgeusia/dysosmia in the first 3 years (n = 55) of operation had a mean age of 54.5 years with a range of 23 to 93 years. Controls analyzed in the same time frame (n = 18) had a mean age of 36.2 years with a range of 20 to 62 years.

Patients with altered chemosensation (dysosmia/dysgeusia) are sampled at the Sensory Clinic located at Thomas Jefferson Medical College; consequently, their mouth air is collected in a 0.5 ℓ Tedlar bags and brought back to the laboratory for analysis.

Patients then donate both resting and stimulated whole mouth saliva samples according to a standard protocol.[30] Following this, subjects collect expired breath (lung air) using a 20 ℓ Tedlar bag.[24] Thirty ml aliquots of the collected lung air and the headspace above saliva are individually sampled for VSC as previously described.[1,12] Following this, the volatiles in the headspace above saliva and the volatiles in the Tedlar bag are collected using the polymeric adsorbent Tenax.[24] Subsequent analysis and quantitation of the volatiles are performed using gas chromatography/mass spectrometry.[12,24,29] These collection, concentration, and structure identification techniques have been used to characterize a number of body odors in our laboratory.[19,24,31]

Patients also undergo sensory and clinical examinations. These include sensory assessments of gustatory and olfactory discrimination and sensitivity,[32] as well as dental and otolaryngology examinations. Consequently, although patients come to us via dental or physical referrals, examinations by our collaborating clinicians are a critical part of our patient evaluation.

Table 2. Individuals Seen by the Analytical Core Facility

	N
Normals	18
Dysgeusic/dysosmic	55
Idiopathic malodor producers	20

Table 3. Presenting Complaints of Patients with Dysguesia and/or Dysosmia

Group	N	Characteristics
1	7	Bad smell (smoky, metallic, musty)
2	11	Burning, tingling, tenderness plus an off-taste (salty-sour)
3	4	Malodor (others detect)
4	5	Taste (sour, metallic, bitter)*
5	3	Taste (salty, bitter, rotten)*
6	3	Smell + taste (sweet)
7	22	Distortion of taste or smell

*Not included in these categories are several patients referred to us with putative chemosensory distortions that were shown to have an obvious clinical reason for their problem. For example, in the first 3 years of operation of our CCRC, 4 patients presented with previously undiagnosed periodontal abscess formation or chronic suppurative pulpitis in concert with abscess formation. In itself, these findings are common, however, correspondence of the clinical disease to a history of a salty taste was overlooked by community dentists and other clinicians. In these patients, resolution of the dental pathology resulted in abatement of the dysgeusia. We believe that the inflammatory exudate produced the salty taste, in itself capricious at times in that inflammatory processes in the mouth are known to suffer exacerbations and remissions. Intervals of dysgeusia in these patients might be interrupted by quiescent periods corresponding to remissions of the quantity or quality of the exudate.

RESULTS

Table 2 lists the number of patients and controls seen in the CCRC Analytical Core Facility in its first 3 years of operation. The presenting complaints for the patients with altered chemosensory function are numerous with either hedonic description (an unpleasant quality) or distortions of normal taste and smell quality being reported. These presenting complaints are listed in Table 3.

The variety of complaints suggest multiple etiologies and/or individual differences in "labels" used by patients to describe their complaints. Catalanatto and Sweeney[33] have suggested that many of these types of complaints (Table 3) may be oral in their origin; however, we found no clinical correlation with diagnosed anatomic disease. Therefore, changes in the patient's oral or systemic chemistry caused by more subtle conditions must then be considered.

The compounds listed in Table 4 were routinely searched

Table 4. Compounds Analyzed by Analytical Core

Mouth Air	Lung Air and Salivary Headspace		Salivary Extract
Hydrogen sulfide	Hydrogen sulfide*	2-Ethyl-1-hexanol	Organic acids
Methyl mercaptan	Methyl mercaptan*	Decanal	Aliphatic C_2-C_{18} acids
Dimethylsulfide*	Dimethylsulfide*	Acetic acid*	Aromatic acids
	Acetone	Propanoic acid	
	Dimethyldisulfide	Isobutyric acid	
	Limonene	Isovaleric acid	
	Pyridine*	Menthol	
	Acetoin*	Aniline*	
	2-methyl pyridine	o-toluidine	
	Octanal	Dodecanol*	
	Dimethyltrisulfide*	Phenol*	
	Nonanal	Tetradecanol	
	Dichlorbenzene*	Caprolactam	
	1-Octen-3-ol*	Indole	
	Benzaldehyde*	p-cresol*	
		Skatole	
		Diphenylamine*	

*Indicates one of the volatiles that discriminates patients with chemosensory dysfunction (Table 3) from normals.

for in the designated sample and quantitated with the aid of standard curves and/or co-injected standards added to the Tenax collection tubes.[24] Chemistry data from each patient and control were examined by discriminate function analysis. This analysis was performed to determine if the patients could be, as a group, discriminated from the normals using the volatile compounds routinely identified in lung air and saliva. Since the ratio of variables to patients is less than 1:2 (1:5 would be ideal), the analysis can only be considered an estimate.

The resultant analysis suggests that a linear combination of 16 variables (volatiles) are needed to adequately separate the 2 groups; these are indicated in Table 4 by an asterisk (*). The volatiles with the highest correlation with the discriminant functions are found in expired lung air: aniline, 1-octen-3-ol, acetoin, and dimethyltrisulfide. Aniline and dimethyltrisulfide are high in the patient population and acetoin and 1-octen-3-ol are high in the normals. The function is 95% efficient in classifying patients and controls into their respective groups. These results are depicted in Figure 2. The top part of Figure 2 shows the distribution of normal subjects while the bottom part shows the distribution of dysgeusic/dysosmic patients. The centroids of the distribution for each group are clearly different ($P < 0.001$). It should be noted that the number of normals (n = 12) and dysgeusic/dysosmic patients (n = 30) is less than found in Table 2. The discriminate function analysis only utilizes completed sets of data. Those normals and patients excluded from the analyses had one or more chemical components missing from their data sets.

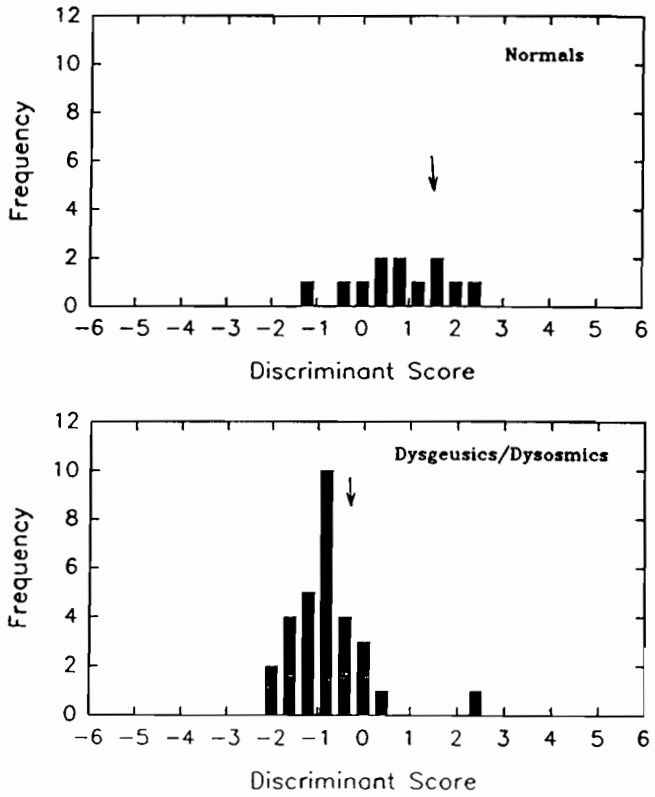

Figure 2. Both the top (Normals) and bottom (Dysgeusic/Dysosmic) of this figure show the distribution of patients within each group along the discriminating axis. The arrow marks the centroid for each distribution. Patients with chemosensory complaints tended to show higher levels of aniline and dimethyltrisulfide in their expired lung air than normals.

The discriminate function analysis only considers the compounds for both groups which distinguish one from the other. Although differences were uncovered by this analysis, the type and number of presenting complaints suggest that there is more than one possible etiology for the chemosensory dysfunctions and that this patient group is nonhomogenous. Further examination of the data from the patient group was performed to see if obvious differences were present.

After dividing the dysgeusic/dysosmic patients into groups as listed in Table 3, there are several volatiles present in the lung air and saliva of one or more of the patient groups which are not seen in normal subjects. The lung air constituents are C_2-C_5 aliphatic acids (acetic, propionic, bu-

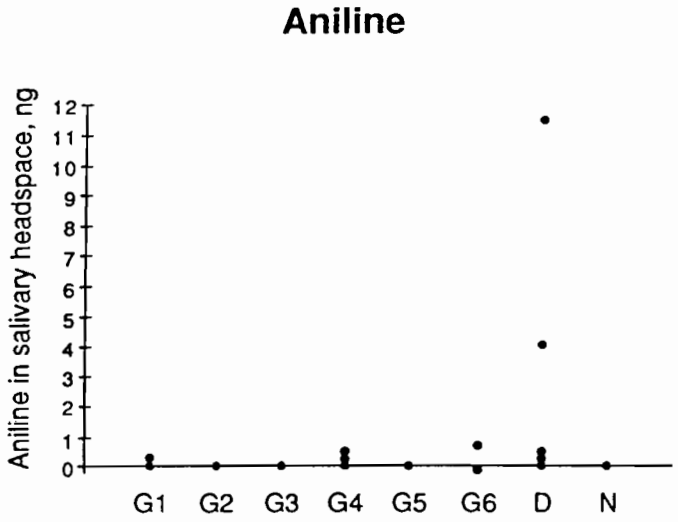

Figure 3. Shows the level (in nanograms/20 L of expired lung air) of aniline in normals (−) and each of the patient groups (by presenting complaints) as discussed in Table 3. Each symbol (*) represents data from one individual.

tyric, 2-methylbutyric, and isovaleric acid) while the salivary constituents are aniline, dimethyldisulfide, and dimethyltrisulfide. The distribution of these compounds in the patients and control group are depicted in Figures 3 and 4.

Both salivary aniline and the lung air aliphatic acids appear more frequently in groups 1 to 4 and the patients with distorted taste and smell. We do not know the origin of these components or how they may be involved with the dysfunction phenomena being observed, but it would be reasonable to expect that an excess of these compounds in the oral cavity might create an unpleasant sensation. When sampled individually, or as a group, these compounds are not pleasant olfactory stimuli.

Patients With Idiopathic Malodor Production. Patients with complaints of malodor production may be separated by presenting complaints (Table 5). One of the patients with documented trimethylaminuria (TMAU) has been discussed in detail in a recent report.[34] In both cases of TMAU, the patients reported a persistent bad "flavor," odor, and/or taste. In these patients, their altered oral sensation appeared to have been caused by a metabolic defect which results in an excess of trimethylamine (TMA, a fishy smelling amine which is a gas at body temperature) also present in sweat, breath, and urine.[35] In normal individuals, TMA is converted in the liver to odorless products (such as trimethylamine N-oxide) that are excreted in the urine and feces. Originally, TMA was thought to result solely from the inability of the liver to convert trimethylamine to trimethylamine N-oxide. This defect appears to be inherited as an autosomal recessive trait and is thought to occur in 1 in 5,000 births.[35] However, a recent paper[36] suggests that some patients with excessive TMA production may suffer from excessive production of this compound by gut bacteria. The persistent foul taste/odor reported by these patients may be due to the presence of trimethylamine; however, excess amounts of other volatiles in the saliva and lung air of these patients are also seen.[34] We could detect the odor of TMA on the saliva/sputum of these patients.

The second group of patients listed in Table 5 are often

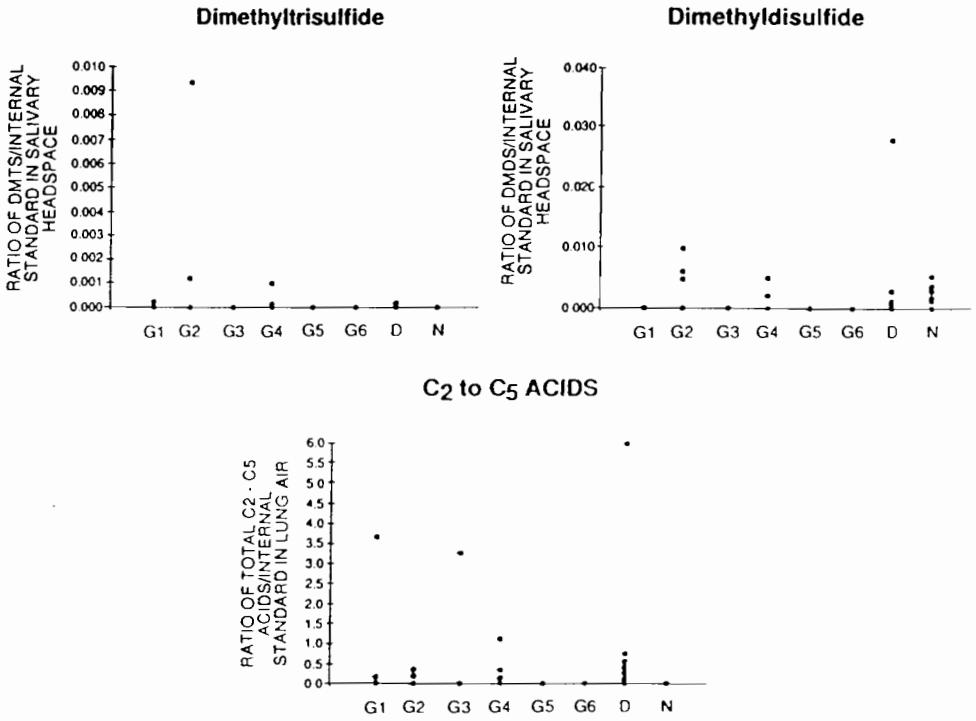

Figure 4. Displays the levels (ratio of compound/injection standard) of C_2-C_5 aliphatic acids, dimethyldisulfide, and dimethyltrisulfide in normals (N) and each of the patient groups (by presenting complaint) as discussed in Table 3. Each symbol (*) represents data from one individual.

Table 5. Persistent, Idiopathis Malodor Producers (N = 20)

Group (N)	Presenting Symptoms	Cause
1 (2)	Foul smell/taste* persistent, long-standing; may vary with diet	Excess trimethylamine caused by trimethylaminuria (TMAU)
2 (11)	Long-standing oral malodor and/or nasal odor†	High levels volatile sulfur compounds in mouth air/saliva and/or expired breath
3 (4)	Oral malodor, bad breath*	No apparent elevation in the components analyzed
4 (3)	Axillary, genital, and/or general body odor‡	

*The odors may or may not be apparent to people near the patient because they are episodic and vary in intensity. Spouses, children, and/or those intimate with the patient often corroborate the complaint of malodor.
†As with the TMAU sufferers, those close to the patient would corroborate the malodor complaint; although many in this group suggested the malodor could be transient. In our clinic these patients presented most often with detectable oral malodor.
‡These patients are seen in collaboration with colleagues in the Department of Dermatology, Obstetrics/Gynecology, and/or Metabolic Disorders, University of Pennsylvania.

Table 6. Mouth Air Volatile Sulfur Compounds (NG/10cc)

Subjects	H_2S	CH_3SH
Normals	4.30 ± 2.19	0.07 ± 0.22
Idiopathic malodor producers	7.46 ± 2.93	0.66 ± 1.14
Individual examples of group 2 subjects		
5004	19.6	0.00
5006	8.53	1.02
5010	8.83	4.55
5017	11.6	6.60

characterized by halitosis evident to those around them even though their oral health is normal. Table 6 lists the values for VSC compounds found in both normals and all patients with idiopathic malodor production.

Several of the patients (Table 5, group 2) show high levels of both H_2S and CH_3SH. The latter appears to be important in imparting a malodorous, stale quality to the patients breath.[1,2] Two patients, 5004 and 5017, were noteworthy in that they produced the largest amounts of total VSC in all patients seen. Oral malodor could be recognized from several feet away. The oral exam of both patients indicated that although they had seen their dentist within the last 6 months, each had moderate plaque deposits, suggesting the need for more frequent prophylaxis and home dental care. The persistence of foul breath in spite of oral prophylaxis prompted us to perform duplicate analysis of each patient's urinary amino acid profiles. The results of these were significant: patient 5004 showed high levels of cysteine while patient 5017 was shown to have elevated cystathionine levels.

These results suggest a sulfur amino acid metabolism problem and the possibility that these patients are heterozygotic for cystinuria and cystathionuria, respectively. Further complicating this problem in patient 5017 was his desire to frequently consume ethnic foods containing high levels of sulfur compounds such as onions, garlic, and broccoli.

In patients such as these, abnormal amounts of sulfur-containing amino acids are available to gut microorganisms to synthesize VSC. These compounds are adsorbed through the gut wall into the circulatory system. Although present in all body fluids they are evident on the person's breath since they pass into lung air due to their volatility.

DISCUSSION

Our results suggest that longstanding complaints of oral malodor and/or foul taste with no apparent oral etiology should not be dismissed by the dentist or physician. Even if referrals to other specialists (ear/nose/throat specialist, gastroenterologist, neurologist) yield negative findings there may be more subtle causes for the chief complaint outside the clinical experience of even experienced specialists.

Data from our clinic have been the first to suggest a relationship between metabolic disorders known to produce an excess of volatile organic compounds with both altered chemosensation and longstanding idiopathic oral malodor production. The paucity of knowledge among medical and dental specialists concerning the occurrence of disorders such as trimethylaminuria may be a source of frustration to the patient who seeks, at least an explanation for their condition.

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